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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/660,434	09/10/2003	Guennadi V. Glinskii	23543-07570	4883

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EXAMINER	
LIN, JERRY	
ART UNIT	**PAPER NUMBER**
1631	

SHORTENED STATUTORY PERIOD OF RESPONSE	MAIL DATE	DELIVERY MODE
3 MONTHS	03/21/2007	PAPER

Please find below and/or attached an Office communication concerning this application or proceeding.

If NO period for reply is specified above, the maximum statutory period will apply and will expire 6 MONTHS from the mailing date of this communication.

Office Action Summary	Application No.	Applicant(s)	
	10/660,434	GLINSKII, GUENNADI V.	
	Examiner	Art Unit	
	Jerry Lin	1631	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *27 December 2006*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-28* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-28* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date *1 page (2/5/2007)*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

1. Applicants' arguments, filed December 27, 2006, have been fully considered and they are not deemed to be persuasive. The following rejections are either reiterated or newly applied as necessitated by amendment. They constitute the complete set presently being applied to the instant application.

Status of the Claims

Claims 1-28 are under examination.

Regarding claims 24-28, the Table 5 was elected as species, and the other tables are withdrawn as being drawn to an unelected species.

Information Disclosure Statement

2. The listing of references in the Search Report is not considered to be an information disclosure statement (IDS) complying with 37 CFR 1.98. 37 CFR 1.98(a)(2) requires a legible copy of: (1) each foreign patent; (2) each publication or that portion which caused it to be listed; (3) for each cited pending U.S. application, the application specification including claims, and any drawing of the application, or that portion of the application which caused it to be listed including any claims directed to that portion, unless the cited pending U.S. application is stored in the Image File Wrapper (IFW) system; and (4) all other information, or that portion which caused it to be listed. In addition, each IDS must include a list of all patents, publications, applications, or other information submitted for consideration by the Office (see 37 CFR 1.98(a)(1) and (b)),

and MPEP § 609.04(a), subsection I. states, "the list ... must be submitted on a separate paper." Therefore, the references cited in the Search Report have not been considered. Applicant is advised that the date of submission of any item of information or any missing element(s) will be the date of submission for purposes of determining compliance with the requirements based on the time of filing the IDS, including all "statement" requirements of 37 CFR 1.97(e). See MPEP § 609.05(a).

Thus the European Search Report and PCT search report has not been considered. If the Applicant would like the Examiner consider the references cited on the search reports, the Examiner recommends that the references be listed on an IDS and that the Applicant supply copies of foreign patents and non-patent references.

Claim Rejections - 35 USC § 112, 2nd Paragraph

3. The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

4. Claims 1-28 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

5. Claim 1 is indefinite because it is unclear what the term “direction” means in line nine. One interpretation of the term is that the common genes have an increased expression in the first sample to second sample and in the third sample to the fourth sample (or decreased expression in the first sample to the second sample and in the third sample to the fourth sample). Another interpretation of the term is that absolute

value of differential expression is the same in the first to second sample and the third to fourth sample.

Response to Arguments

6. The Applicant has amended the instant claim by removing "the" before term "direction." However, it remain unclear what the term "direction" means. The removal of the term "the" does not clarify the meaning of this term.

7. Claims 24-28 are also unclear because the recited tables include genes that are insufficiently described in the specification. Table 5 lists Affymetrix Probe Set ID, LocusLink Identifier, and a Description for each gene. However, the specification does not include any sequence listing that indicates what the gene is. Furthermore, upon consultation with the Scientific and Technical Information Center, the instant claims are not searchable, since the information associated with the Affymetrix Probe Set ID and LocusLink Identifier are frequently updated and the information changes. Because the information is updated frequently, it is unclear what subject matter is claimed and is to be searched.

Response to Arguments

8. The Applicant has amended the specification by including the sequence listing of each of the genes recited in the Tables. Each table also states that the Seq ID Nos are assigned "in order or appearance." It is unclear what is meant by "in order or appearance." For example, one interpretation is that "in order" may mean reading the table vertically down each column first before moving to the next column. Another

interpretation is that the rows are read first before moving to the next row. In addition, it is unclear the alternative method of reading the table is under "or appearance." The Examiner requests some clarification so that examination of these sequences can continue.

Claim Rejections - 35 USC § 103

9. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

10. Claims 1-23 are rejected under 35 U.S.C. 103(a) as being unpatentable over Backert et al. (Int. J. Cancer (1999) Volume 82, pages 868-874) in view of Bertucci et al. (Human Molecular Genetics (2000) Volume 9, Number 20, pages 2981-2991).

The instant claims are drawn to identifying a subset of genes using a correlation coefficient calculated from gene expression data.

Regarding 1, Backert et al. teach using two samples that different with respect to phenotype and determining a reference set of genes (page 869, left column; page 870, paragraph bridging left and right column), identifying a second reference set of expressed genes from a third and fourth sample (page 870, right column, second full paragraph); identifying a concordance set of expressed genes (page 870, right column, bottom full paragraph). Furthermore, Backert et al. recorded the genes identified in the

description of the genes that have lowered expression (page 870, right column, bottom full paragraph).

However, Backert et al. do not teach determining a correlation coefficient that exceeds a predetermined value.

Bertucci et al. teaches determining the correlation coefficient that exceed a predetermine value for correlating genes (page 2987, right column, 2nd full paragraph).

It would have been obvious to one of ordinary skill in the art at the time of the invention to combine the methods of Backert et al. with Bertucci et al. to gain the advantage of determining the reproducibility of experiments. One of the challenges that face gene expression experiments is the precision of the equipment used in those experiments. Given the same experiment, the equipment may produce different results. Given the uncertainty of the equipment as well as the need to compare data from different sources, one of ordinary skill in the art would seek to verify the reproducibility of experiments to ensure that their interpretation of the data is correct. Backert et al. recognized the need to find determine the accuracy of gene expression experiments (page 871, right column, under discussion). Bertucci et al. teaches a method of determining the accuracy of gene expression using a correlation coefficient (page 2987, right column, 2nd full paragraph). Given that Backer et al. recognizes the need for determining the accuracy of a gene expression experiment, and Bertucci et al. provides for such a need, one of ordinary skill in the art would be motivated to combine the methods of Backert et al. and Bertucci et al. to ensure that the gene expression data was accurate.

Regarding claims 2-6, Bertucci et al. teach determining a correlation coefficient (page 2987, right column, 2nd full paragraph); logarithmically transforming the differentials (page 2987, right column, 3rd full paragraph); wherein the correlation coefficient has an absolute value greater than 0.98 (page 2987, right column, 2nd full paragraph).

Regarding claims 8-11, Bertucci et al. teach wherein the gene expression data is cDNA or RNA quantification data (page 870); wherein the sample comprises of a cell line, which is a tumor cell line (page 869, left column, top).

Regarding claims 16-19, Bertucci et al. teach wherein the sample is from a patient, a healthy donor, is a tumor cell, or from the colon (paragraph bridging pages 869-867).

Regarding claim 20, Bertucci et al. teach where the phenotype is selected from lymph node status (page 2983, left column, bottom section).

Regarding claim 21, Bertucci et al. teach where a plurality of independent samples is used for each sample (paragraph bridging page 869-870); and where the differential is an average over the sample (page 870, Table II).

Regarding claim 22, Bertucci et al. teach determining a second correlation coefficient with a positive sign that establishes a positive correlation with a phenotype (page 2983, right column, first full paragraph).

Regarding claim 23, Bertucci et al. teach that ERBB2 had the highest correlation of the genes tested (page 2983, first full paragraph) and since its correlation was the

highest its correlation was the most reliable indication of cancer (abstract; page 2985, left column, bottom paragraph – right column, top paragraph).

It would have been obvious to one of ordinary skill in the art to combine the methods of Backert et al. and Bertucci et al. to determine the accuracy of the experiments. Given the uncertainty of the equipment as well as the need to compare data from different sources, one of ordinary skill in the art using Backert et al.'s method would be interesting in verifying the accuracy of the experiments. Bertucci et al. teach several methods of determining the accuracy using gene expression data of different samples and phenotypes of an experiment, such as determining the correlation coefficient and using independent samples. Thus one of ordinary skill in the art would be motivated to combine the methods of Bertucci et al. and Backert et al. to determine accuracy of Backert et al.'s experiments.

Response to Arguments

11. The Applicant has responded to this rejection by first stating that neither Backert et al. or Bertucci et al. teach identifying a first reference set of expressed genes from a first and second sample or identifying a second reference set of genes from a third and fourth sample independent of the first and second sample. The Examiner disagrees.

Backert et al. measures the expression of genes from normal cell (first sample) and carcinomatous (second sample) colonic cell lines (page 870, paragraph bridging first and second column). The identification of genes that are differentially expressed (3-fold larger or smaller than the normal cells) were interpreted to be the first reference

set. Backert et al. then uses a another set of samples of normal cells (third sample) and carcinoma cells (fourth sample) to determine another set of genes (second reference set) (page 870, right column). Backert et al. then compares the two reference sets and determines a concordance set (i.e., a set of genes that are common to both the first reference set and second reference set) (page 870, right column). Even if Backert et al. was using one set to verify another set, this interpretation is well within the scope of the instant claims. Finally Backert et al. teach identifying a subset within the concordance set such as 5 genes that were lowered significantly in both cell lines (page 870, right column).

The Applicant also points out that Backert et al. does not teach that the third and fourth samples are independent from the first and second sample. However, instant claims have not such limitation, and Backert et al. do teach that the first and second samples are independent from the third and fourth samples. As the Applicant points out, Backert et al. analyzes cell lines (first and second sample) and then compares them to human tissue (third and fourth sample). Since the source of the samples is different, it would indicate that the samples are independent.

The final point the Applicant raises, is that Bertucci et al. does not teach determining a correlation coefficient that exceeds a predetermined value. The Examiner disagrees. While it is true that Bertucci et al. teach testing for reproducibility, the tests Bertucci et al. performed also indicates that the 2-fold expression difference as significantly differential (page 2987, right column, 2nd full paragraph). Thus the test

correlates that genes between the two sets and indicates the difference in expression is significantly differential.

The Applicant has also amended the instant claims to include recording a listing of the genes identified. Backert et al. recorded the genes identified in the description of the genes that have lowered expression (page 870, right column, bottom full paragraph).

The rejection is maintained and necessitated by amendment.

12. Claims 12 and 13 are rejected under 35 U.S.C. 103(a) as being unpatentable over Backert et al. (Int. J. Cancer (1999) Volume 82, pages 868-874) in view of Bertucci et al. (Human Molecular Genetics (2000) Volume 9, Number 20, pages 2981-2991) further in view of Young et al. (US #2005/0255588 A1).

The instant claims are drawn to identifying a subset of genes using a correlation coefficient calculated from gene expression data and using samples comprising omnipotent or pluripotent cells.

Backert et al. and Bertucci et al. are applied as above.

However, neither Backert et al. nor Bertucci et al. teach using pluripotent or omnipotent stem cells.

Young et al. teach creating samples of pluripotent or omnipotent stem cells (page 3, paragraph 0019-0020).

It would have been obvious to one of ordinary skill in the art at the time of the invention to use the cell lines described in Young et al. with the methods of Backert et

al. and Bertucci et al. The motivation to combine Backert et al. with Bertucii et al. is provided above. It is recognized in the art the use of stem cells could potentially provide many new applications in science and medicine (Young et al., page 3, paragraph 0015-0016). However, it is unclear genes are expressed to maintain a cell as a stem cell. Thus one of ordinary skill in the art seeking to understand the gene expression of stem cells would be motivated to determine what genes are differentially expressed that correspond to the stem cell phenotype. Backert et al. provide a method of identifying the correct identification of the differences in gene expression between different cell lines (Backert et al., page 873, right column, bottom). Backert et al.'s method could identify the differences in gene expression in a stem cell as compared to other cells. Thus one of ordinary skill in the art seeking to understand the gene expression of stem cells would be motivated to take the sample cell lines disclosed by Young et al. and use those samples in the method provided by Backert et al.

Response to Arguments

12. The Applicant has responded to this rejection by arguing that Backert et al. and Bertucci et al. do not teach all the limitations of claim 1. See above for the Examiner's response.

The rejection is maintained and necessitated by amendment.

Conclusion

Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL**. See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

Contact Information

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Jerry Lin whose telephone number is (571) 272-2561. The examiner can normally be reached on 10:00-6:30, M-F.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Irem Yucel can be reached on (571) 272-0781. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

JL

MICHAEL BORIN, PH.D
PRIMARY EXAMINER